PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Paediatrics Open. The paper was subsequently accepted for publication at BMJ Paediatrics Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of Cerebral Palsy with Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder in Children: A Large-Scale Nationwide Population-Based Study
AUTHORS	Chen, Qiang Chen, Mingwu Bao, Wei Strathearn, Lane Zang, Xiaodong Lun, Meng Xu, Guifeng

VERSION 1 - REVIEW

REVIEWER	Magnus Påhlman
REVIEW RETURNED	23-Nov-2023

GENERAL COMMENTS	Thank you for putting in effort in the research about the association of cerebral palsy with autism and ADHD. This is an important topic since this association is real and children with cerebral palsy often have these associated impairments, often more disabling than the motor disorder. You have analysed a huge group of children. The methodology is sound, the presentation is clear, and the manuscript is well written. However, there is a need for revision and updating. My main concern is that the Introduction starts from a point relevant some years ago. There is a lack of more updated references. It is striking that the authors refer to 2017 as recently (page 7, third row, reference 5). New research has been presented the last years adding to the knowledge. One of your main references is the systematic review by Craig et al from 2019. One track to follow for updating is that review having been referred to 34 times according to Scopus. Already in the first paragraph in the Introduction I think you should use more recent data about cerebral palsy worldwide (McIntyre et al 2022, Global prevalence of cerebral palsy: A systematic analysis). In the end of the Introduction you state that "there has been no quantitative assessment about the association of cerebral palsy with ASD and ADHD". To my knowledge there are one article from Norway (Hollung et al 2019, Comorbidities in cerebral palsy: a patient registry study) and one from Denmark (Rackauskaite et al 2019, Prevalence of mental disorders in children and adolescents with cerebral palsy: Danish nationwide follow-up

	study) presenting data about this. Another important point about methodology is how these numbers about the prevalence's of cerebral palsy, ASD and ADHD relate to how common these impairments really are. This is not in the field of this study to answer but should be pointed out as a limitation in the Discussion. The numbers of cerebral palsy are most likely more accurate than the numbers of ASD and ADHD. Under-identification of these neurodevelopmental disorders due to overshadowing of the motor disorder is mentioned as substantial in several reports. Finally, some small aspects. In Methods you describe the NHIS and write that it has "a relatively high response rate". Please specify for better understanding. In the Discussion you mention several explanations for the association between cerebral palsy and ASD/ADHD. You could add that medial cerebral artery infarction has been reported as a risk factor for both ASD and ADHD (as well as intellectual disability and epilepsy). In the limitations you mention that gold standard methods are not suitable. Some may argue that the gold standard for diagnosing ASD and ADHD is an experienced clinician, not specific instruments. And you lift the lack of subtypes of cerebral palsy. I would also add the gross motor function (GMFCS level) as important in the context. I hope you find my comments and suggestions helpful in improving your manuscript., mainly regarding the Discussion. Please revise and update.

REVIEWER	Dr. Russell S. Kirby University of South Florida, College of Public Health
REVIEW RETURNED	27-Nov-2023

GENERAL COMMENTS	In this manuscript, the authors use data from the US National Health Interview Survey to examine to co-occurrence of autism spectrum disorder and ADHD in children with a parent-reported diagnosis of cerebral palsy. The analysis seems appropriate, but one wonders about the added-value of this report given that the NHIS has been used for similar purposes in the past and this study does not update those results but rather incorporates them into a 20+ year perspective that does not account for year of birth. Also, the authors make no reference to work from the CDC ADDM Network, which conducted population-based surveillance of ASD and cerebral palsy in several US communities, focusing on 8-year old children. Their findings should at least be compared with those in this report. The issue of time is important, as there have been changes to diagnostic criteria for ASD over time, and also to some extent criteria for cerebral palsy. Children who were included in the sample for the earlier years likely had a lower overall prevalence of ASD and this should be taken into account. In addition to including reference to additional US-based work on prevalence and co-occurrence of cerebral palsy with other developmental conditions, the tables could also be improved. In Table 1, the column headings could be improved. In the headings, include N and (weighted %) for each column. Instead of adding the

	N in the title, indicate its for US children 3-17, with the year range. Also, round all percents to a single decimal. And, while epidemiologists argue this point, this reviewer would prefer that the percents in each row sum to 100.0 rather than summing across all strata for each variable. The family income variable isn't clear - presumably this is in relation to 100% of the federal poverty level? Include data on the prevalence of ASD and ADHD, and by year of birth. In Table 2, adjust for year or groups of years of birth. This reviewer would like to see the adjusted odds for the strata of each covariate. Many of the references for context are fairly old. Consider a recent clinical update: Michael-Asalu, Abimbola, Genevieve Taylor, Heather Campbell, Latashia-Lika Lelea, Russell S. Kirby, "Cerebral Palsy: Diagnosis, Epidemiology, Genetics and Clinical Update", Advances in Pediatrics, 66 (July 2019), 189-208.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

Comment #1: This is an important topic since this association is real and children with cerebral palsy often have these associated impairments, often more disabling than the motor disorder. The authors have analysed a huge group of children. The methodology is sound, the presentation is clear, and the manuscript is well written. However, there is a need for revision and updating. My main concern is that the Introduction starts from a point relevant some years ago. There is a lack of more updated references. It is striking that the authors refer to 2017 as recently (page 7, third row, reference 5). New research has been presented the last years adding to the knowledge. One of your main references is the systematic review by Craig et al from 2019. One track to follow for updating is that review having been referred to 34 times according to Scopus. Already in the first paragraph in the Introduction. I think you should use more recent data about cerebral palsy worldwide (McIntyre et al 2022, Global prevalence of cerebral palsy: A systematic analysis).

Response #1: We thank the reviewer for the comments and suggestions. We have used the more recent data about cerebral palsy worldwide (McIntyre et al by 2022), updated the references with more recent publications (for example, the articles by Friedman et al 2022, Morgan et al 2021, Pahlman et al 2021), and removed the word "recently" for the reference published in 2017 (Page 5, Line 9).

Comment #2: In the end of the Introduction you state that "there has been no quantitative assessment about the association of cerebral palsy with ASD and ADHD". To my knowledge there are one article from Norway (Hollung et al 2019, Comorbidities in cerebral palsy: a patient registry study) and one from Denmark (Rackauskaite et al 2019, Prevalence of mental disorders in children and adolescents with cerebral palsy: Danish nationwide follow-up study) presenting data about this.

Response #2: We thank the reviewer for the comment. We have carefully reviewed the references that the reviewer mentioned: the Hollung et al 2019 paper and the Rackauskaite et al 2019 paper. Moreover, we have performed a thorough literature search for studies linking cerebral palsy to ASD and ADHD in children. Accordingly, we have reworded the sentence in the introduction into "While previous studies have noted a higher co-occurrence of ASD and ADHD in children with cerebral palsy, very few studies have quantified the association (i.e., odds ratio or risk ratio) of cerebral palsy

with ASD and ADHD", and cited the relevant references (Page 5, Line 13-15), we have also discussed the relevant research in the discussion (Page 10, Line 3-16).

Comment #3: Another important point about methodology is how these numbers about the prevalence's of cerebral palsy, ASD and ADHD relate to how common these impairments really are. This is not in the field of this study to answer but should be pointed out as a limitation in the Discussion. The numbers of cerebral palsy are most likely more accurate than the numbers of ASD and ADHD. Under-identification of these neurodevelopmental disorders due to overshadowing of the motor disorder is mentioned as substantial in several reports.

Response #3: We thank the reviewer for the thoughtful comment. We have added this consideration in the discussion as a limitation (Page 11, Line 19-20).

Comment #4： In Methods you describe the NHIS and write that it has "a relatively high response rate". Please specify for better understanding.

Response #4: We have added more details about the response rate as the reviewer suggested (Page 6, Line 9-11).

Comment #5： In the Discussion you mention several explanations for the association between cerebral palsy and ASD/ADHD. You could add that medial cerebral artery infarction has been reported as a risk factor for both ASD and ADHD (as well as intellectual disability and epilepsy).

Response #5: Added as the reviewer suggested (Page 11, Line 4).

Comment #6： In the limitations you mention that gold standard methods are not suitable. Some may argue that the gold standard for diagnosing ASD and ADHD is an experienced clinician, not specific instruments. And you lift the lack of subtypes of cerebral palsy. I would also add the gross motor function (GMFCS level) as important in the context.

Response #6: We thank the reviewer for the thoughtful suggestions. We have removed the wording of "gold standard" methods (Page 11, Line 17-18), and we also have added the GMFCS level as important in the discussion (Page 11, Line 20-23).

Reviewer #2

Comment #1: In this manuscript, the authors use data from the US National Health Interview Survey to examine to co-occurrence of autism spectrum disorder and ADHD in children with a parent-reported diagnosis of cerebral palsy. The analysis seems appropriate, but one wonders about the added-value of this report given that the NHIS has been used for similar purposes in the past and this study does not update those results but rather incorporates them into a 20+ year perspective that does not account for year of birth. Also, the authors make no reference to work from the CDC ADDM Network, which conducted population-based surveillance of ASD and cerebral palsy in several US communities, focusing on 8-year old children. Their findings should at least be compared with those in this report.

Response #1: We thank the reviewer for the comment. In this study, we pooled data from 20+ survey years, because a large sample size is required for a robust estimation of the association between relatively rare conditions such as cerebral palsy and autism spectrum disorder. The large sample size is a strength of using the NHIS data. We have also added description about previous work about cerebral palsy and ASD from the CDC ADDM Network (Christensen et al. Dev Med Child Neurol. 2014) (Page 5, Line 5-9).

Comment #2： The issue of time is important, as there have been changes to diagnostic criteria for ASD over time, and also to some extent criteria for cerebral palsy. Children who were included in the sample for the earlier years likely had a lower overall prevalence of ASD and this should be taken into account.

Response #2: We thank the reviewer for the wise suggestion. Changes of diagnostic criteria over time is indeed a concern for population-based study across a long period. Because there is no information on the specific age of the diagnoses of cerebral palsy, ASD or ADHD in this study, we could not compare the odds ratios of ASD and ADHD before and after criteria changes. However, in view of the reviewer's comment, we performed additional analyses by separating the survey years into two periods (i.e., 1997-2009 and 2010-2018). The results appeared similar across those two periods (**Table R1** as follows). Given that cerebral palsy is a rare condition, the sample size does not allow us separating the data into more periods for the association analyses. We have also added the issue of changing diagnostic criteria over time as a limitation in the discussion (Page 12, Line 2-4).

Table R1. Association of cerebral palsy with ASD and ADHD in US children aged 3-17 years, by periods of survey years.

	OR (95% CI)		P-value
	Without CP	**With CP**	
ASD			
Period 1			
No. of cases/total	387/91542	6/356	
Multivariable model	1.00 (reference)	4.95 (1.78-13.77)	<0.001
Period 2			
No. of cases/total	1574/85755	30/246	
Multivariable model	1.00 (reference)	5.36 (3.28-8.77)	<0.001
ADHD			
Period 1			
No. of cases/total	5795/91542	59/356	
Multivariable model	1.00 (reference)	2.29 (1.55-3.38)	<0.001
Period 2			
No. of cases/total	7797/91542	46/246	
Model	1.00 (reference)	1.70 (1.04-2.78)	<0.001

Multivariable model adjusted for age, sex, race/ethnicity, family highest education level, ratio of family income to the federal poverty level, geographic region.

Period 1: survey year 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2008, and 2009;

Period 2: survey year 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, and 2018.

Comment #3: In addition to including reference to additional US-based work on prevalence and co-occurrence of cerebral palsy with other developmental conditions, the tables could also be improved. In Table 1, the column headings could be improved. In the headings, include N and (weighted %) for each column. Instead of adding the N in the title, indicate its for US children 3-17, with the year range. Also, round all percents to a single decimal. And, while epidemiologists argue this point, this reviewer would prefer that the percents in each row sum to 100.0 rather than summing across all strata for each variable. The family income variable isn't clear - presumably this is in relation to 100% of the federal poverty level? Include data on the prevalence of ASD and ADHD, and by year of birth.

Response #3: We thank the reviewer for careful checking. We have improved the tables according to the suggestions. The family income variable refers to the ratio of family income to federal poverty level. We have clarified this in the revised Table. We did not change the table into each row summing to 100.0 because it is a common practice to sum to 100.0 across all strata for each variable.

Comment #4 : In Table 2, adjust for year or groups of years of birth. This reviewer would like to see the adjusted odds for the strata of each covariate.

Response #4: In the table 2 models, year of age was adjusted as a continuous variable, and we performed a stratified analyses for age, sex and race in the table 3. Also, for the reviewer's reference, we showed the adjusted odds for ASD and ADHD of each covariate (**Table R2 and Table R3** as follows).

Table R2. Association of cerebral palsy with ASD in US children aged 3-7 years, with odds ratios of each covariate.

Variables	Odds Ratio (95% CI) of ASD	
	Adjusted Model 1	**Adjusted Model 2**
Cerebral palsy	5.29 (3.39-8.26)	5.07 (3.25-7.91)
Age, year	1.00 (0.98-1.01)	1.00 (0.99-1.02)
Sex, male vs female	3.47 (3.00-4.00)	3.47 (3.00-4.00)
Race/ethnicity		
Hispanic		0.89 (0.76-1.04)
Non-Hispanic White		1.00 (reference)
Non-Hispanic Black		0.95 (0.76-1.18)
Other		1.09 (0.89-1.34)
Family highest education level		
Less than high school		1.00 (reference)
High school		1.91 (1.53-2.39)
College or higher		2.13 (1.77-2.57)
Ratio of family income to the federal		

poverty level	
< 1.0	1.00 (reference)
1.0-1.9	0.99 (0.81-1.21)
2.0-3.9	0.77 (0.63-0.94)
>=4.0	0.64 (0.53-0.77)
Geographic region	
Northeast	1.00 (reference)
Midwest	0.83 (0.69-1.00)
South	0.81 (0.67-0.99)
West	0.87 (0.72-1.05)

Table R3. Association of cerebral palsy with ADHD in US children aged 3-7 years, with odds ratios of each covariate.

Variables	Odds Ratio (95% CI) of ADHD	
	Adjusted Model 1	**Adjusted Model 2**
Cerebral palsy	2.10 (1.57-2.82)	1.95 (1.43-2.66)
Age, year	1.11 (1.11-1.12)	1.12 (1.11-1.12)
Sex, male vs female	2.56 (2.44-2.70)	2.60 (2.46-2.73)
Race/ethnicity		
Hispanic		0.48 (0.45-0.51)
Non-Hispanic White		1.00 (reference)
Non-Hispanic Black		0.69 (0.65-0.74)
Other		0.61 (0.55-0.67)
Family highest education level		
Less than high school		1.00 (reference)
High school		1.30 (1.20-1.41)
College or higher		1.16 (1.08-1.24)
Ratio of family income to the federal poverty level		
< 1.0		1.00 (reference)
1.0-1.9		0.73 (0.68-0.79)
2.0-3.9		0.55 (0.51-0.59)
>=4.0		0.51 (0.47-0.55)

Geographic region	
Northeast	1.00 (reference)
Midwest	1.10 (1.03-1.18)
South	1.28 (1.19-1.37)
West	0.81 (0.75-0.87)

Comment #5 : Many of the references for context are fairly old. Consider a recent clinical update: Michael-Asalu, Abimbola, Genevieve Taylor, Heather Campbell, Latashia-Lika Lelea, Russell S. Kirby, “Cerebral Palsy: Diagnosis, Epidemiology, Genetics and Clinical Update”, Advances in Pediatrics, 66 (July 2019), 189-208.

Response #5: We thank the reviewer for the comment. We have reviewed and cited the recommended reference (reference #3). Moreover, we have performed a systematic literature search and updated several references in view of the reviewer’s comments.

VERSION 2 – REVIEW

REVIEWER	Magnus Påhlman
REVIEW RETURNED	20-Feb-2024

GENERAL COMMENTS	Thank you for revising this interesting manuscript. And thank you for meeting all comments very clearly and meticulously. The changed manuscript is now more up-to-date, reflecting the latest research in the field. I have no other comments than that the references should be written in the same style with the same number of authors in a consistent way.

VERSION 2 – AUTHOR RESPONSE

None